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EXAMINER	
BOWMAN, AMY HUDSON	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/574,129	LI ET AL.	
	Examiner	Art Unit	
	AMY BOWMAN	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 September 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-36,38-42,45-59 and 62-65* is/are pending in the application.

4a) Of the above claim(s) *1-35,64 and 65* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *36,38-42,45-59,62 and 63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *31 March 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Newly submitted claims 64 and 65 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Newly added claims 64 and 65 are directed to siRNA molecules comprising SEQ ID NOs: 5 and 6, respectively. However, applicant has already received an action on the merits directed to siRNA molecules comprising SEQ ID NO: 7. As explained in the office action mailed on 3/24/08, the broad claims are not directed to a specific siRNA sequence and the full scope was examined. However, claim 44 recited a specific siRNA sequence (SEQ ID NO: 7) and was examined as the elected siRNA (now recited in claim 36).

The sequences of claims 36, 64, and 65 are not considered to constitute proper genus, as each sequence is structurally unique. Each sequence is considered to be unrelated, since each sequence is structurally and functionally independent for the following reasons: each sequence has a unique nucleotide sequence, each of the sequences do not contain a common structural core, and each sequence represents a separate region of a target, wherein siRNA molecules directed to each of the specific regions are structurally distinct based upon separate and distinct nucleotide sequences. Although each of the siRNA sequences comprises nucleotides, it is the sequence of such nucleotides that defines the activity of each specific siRNA. As such the genus of sequences in the claims is not considered to constitute proper genus, and therefore are subject to restriction. Furthermore, a search of more than one of the sequences claimed presents an undue burden on the Patent and Trademark Office due to the

complex nature of the search and corresponding examination of each. To search for any one of the specific siRNA molecules would not necessarily return art against any of the other siRNA molecules. Therefore, to search for more than one of the siRNA molecules in the same application presents an undue search and corresponding examination.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 64 and 65 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claims 1-35, 64, and 65 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 1/4/08.

Applicant's amendments and/or arguments filed 9/24/08, with respect to the rejection(s) of claim(s) under 35 USC 112, 35 USC 102, and 35 USC 103(a) have been fully considered and are persuasive. Therefore, the rejections have been withdrawn. However, upon further consideration, a new ground(s) of rejection is made as set forth below.

New Rejections

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 36, 38-42, 45-59, 62, and 63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reich et al. (WO 2004/042024 A2), in view of Fosnaugh et al.

(US 2003/0143732 A1), Elbashir et al. (The EMBO Journal, Vol. 20, No. 23, pages 6877-6888, 2001), Tuschl et al. (The siRNA user guide, 8/26/01 (on-line), retrieved 1/31/02, Max Planck Institute for Biophysical Chemistry, pages 1, 3, and 5, http://www.mpibpc.gwdg.de/abteilungen/100/105/siRNAuserguide.pdf), and Holen et al. (Nucleic Acids Research, 2002, Vol. 30, No. 8, pages 1757-1766).

It is noted that the Reich et al. and Fosnaugh et al. references are of record and cited on the PTO-892 mailed on 3/24/08.

The instant claims are directed to a small interfering RNA (siRNA) molecule that down regulates expression of a hypoxia-inducible factor 1α (HIF-1α) gene by RNA interference. The claims are further directed to structural requirements of the siRNA, linkers, modifications, terminal caps, vectors, and cells comprising the vectors.

Reich et al. teaches siRNA molecules that target HIF-1α mRNA and inhibit the expression of the HIF-1α gene via RNA interference (see abstract and page 3, for example). Reich et al. teach siRNA and pharmaceutical compositions thereof which target HIF-1α (see page 3). Reich et al. teach that the siRNA molecules have a first strand that is the same nucleotide sequence as a portion of the HIF-1α mRNA sequence and have a second strand of the siRNA duplex that is complementary to both the first strand of the RNA duplex and the same portion of the HIF-1α mRNA. (see page 4). The siRNA duplexes are about 17 nucleotides to 29 nucleotides in length, more preferably about 19 to about 25 nucleotides in length (see page 4). Reich et al. teach suitable human HIF-1α target sequences on pages 9, 10 and 25.

Reich et al. teach that the siRNA can comprise two separate strands or can comprise a single molecule in which two complementary portions are base-paired and are covalently linked by a single-stranded hairpin area (see page 5), meeting the instant limitation of a nucleotide linker.

Reich et al. teach that the siRNA can contain modifications of one or more ribonucleotide bases and can contain one or more deoxyribonucleotide bases (see page 5). Reich et al. teach that the siRNA can be altered by the addition of non-nucleotide material, such as to the ends of the siRNA or to one or more internal nucleotides of the siRNA, meeting the instant limitation of a terminal cap. Reich et al. teach that the siRNA can be modified with modifications that make the siRNA resistant to nuclease digestion (see page 7).

Reich et al. teach that the siRNA can also comprise a 3'-overhang on one or both strands and that is 1 to 6 , more preferably 1 to 5, more preferably 1 to about 4, more preferably about 2 to about 4 nucleotides in length (see pages 7 and 8). The overhangs can be modified with dithymidylic acid (TT) or diuridylic acid (UU). Reich et al. teach that in order to enhance stability of the siRNA, the 3' overhangs can be stabilized against degradation by substitution by modified analogues (see page 8).

Reich et al. teach that the siRNA can be expressed from plasmids using any suitable promoter either as two separate, complementary RNA molecules or as a single RNA molecule with two complementary regions (see page 11). Reich et al. teach that the siRNA can be expressed from recombinant viral vectors and delivered to human cells (see page 12, for example). The siRNA molecules can be expressed from a

recombinant viral vector either as two separate complementary nucleic acid molecules or as a single nucleic acid molecule with two complementary regions. The viral vector can be derived from adenovirus (see page 13).

Reich et al. teach compositions comprising the siRNA molecules and pharmaceutically acceptable carriers (see claim 28).

Reich et al. do not teach siRNA molecules wherein the sense region comprises instant SEQ ID NO: 7 and the antisense region comprises the reverse complement of SEQ ID NO: 7.

Although Reich et al. teaches utilizing nucleotide linker hairpin regions, Reich et al. do not teach non-nucleotide linkers. Although Reich et al. teaches modifying siRNA molecules to enhance resistance to nuclease digestion, Reich et al. do not specifically teach phosphorothioate nucleotides, universal bases ribonucleotides, or acyclic nucleotides.

Fosnaugh et al. teach siRNA molecules assembled from two separate fragments, wherein one fragment comprises the sense region and the other fragment comprises the antisense region. The fragments can be covalently connected via a linker molecule, wherein the linker molecule can be a polynucleotide linker or a non-nucleotide linker. The siRNA molecules can comprise modified purines or pyrimidines. Fosnaugh et al. teach phosphorothioates at the 3' end of the antisense region, one to five phosphorothioates at the 5' end of the antisense region, and modifications to the 3' terminal overhangs including universal bases or acyclic nucleotides. Fosnaugh et al. teach that chemical modifications of siRNA constructs dramatically increase serum

stability, improve the stability of the interaction with target RNA sequences, and improve nuclease resistance.

Elbashir et al. teach that duplexes of 21-23 nucleotide RNAs are the sequence-specific mediators of RNA interference. Elbashir et al. teach that duplexes of 21 nt siRNAs with 2 nt 3' overhangs are the most efficient triggers of sequence-specific mRNA degradation (see abstract). Elbashir et al. teach duplexes with overhangs as well as blunt ended duplexes that resulted in RNAi activity (see Figure 1, for example). Elbashir et al. teach duplexes wherein each strand is 19 nucleotides in length (see Figure 2, for example). Elbashir et al. teach that these elements provide a rational basis for the design of siRNAs in future gene targeting experiments (see abstract).

Tuschl et al. teach selection guidelines for siRNA duplexes based upon a target mRNA sequence. Tuschl et al. teach that the most efficient silencing was obtained with siRNA duplexes composed of 21-nt sense and antisense strands, paired in a manner to have a 2-nt 3' overhang. Tuschl et al. teach selection of target regions, guidelines in selecting preferred siRNAs directed to that target and blast search comparison of the resultant siRNA molecules to ensure specificity.

Holen et al. teaches synthesis of several siRNAs against different sites on the same target mRNA, wherein the siRNAs demonstrated striking differences in silencing efficiency (see abstract). Holen et al. walked siRNAs in three nucleotide increments to determine the effect on silencing efficiency (see Figure 2), thus demonstrating that siRNA activity is routinely optimized by shifting target position across the mRNA sequence. The siRNAs resulted in varying activity, although each did result in silencing.

It would have been obvious to one of ordinary skill in the art to incorporate the specific structural configurations and chemical modifications of the siRNAs of Fosnaugh et al. into the siRNA molecules specific for HIF-1α of Reich et al., wherein the sense region comprises instant SEQ ID NO: 7 and the antisense region comprises the reverse complement thereof.

One would have been motivated to incorporate the specific structural configurations and chemical modifications of the siRNAs of Fosnaugh et al. into the siRNA molecules specific for HIF-1α of Reich et al. because Reich et al. teaches the concept of incorporating chemical modifications to increase siRNA resistance to nuclease digestion and incorporating a hairpin configuration. Since Reich et al. teach these elements, one would have certainly been motivated to incorporate other linkers or chemical modifications that were known to add the same benefits to siRNA molecules, as taught by Fosnaugh et al. Fosnaugh et al. teach that chemical modifications of siRNA constructs dramatically increase serum stability, improve the stability of the interaction with target RNA sequences, and improve nuclease resistance.

It would have been prima facie obvious to perform routine optimization to determine the optimal structural configuration (i.e. presence of linkers) and optimal chemical modifications of the siRNA molecules, as noted in *In re Aller*, 105 USPQ 233 at 235,

> More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the particular chemical modifications or linkers used was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

It would have been prima facie obvious to perform routine optimization to walk the known HIF-1α target sequence to design any given siRNA against the sequence in view of the guidelines taught by Elbashir et al. and Tuschl et al. It was known in the art that the activity of a siRNA duplex can be optimized by shifting the target sequence, as evidenced by Holen et al.

Since the target sequence was known and it was known to target HIF-1α with siRNA molecules, as taught by Reich et al., one would have been motivated to apply the siRNA guidelines of Elbashir et al., Tuschl et al., and Holen et al. to design optimal siRNAs directed to the instant target sequence.

Furthermore, one would have been motivated to design the siRNA to have the structural characteristics set forth by Elbashir et al., such as overhangs and preferred lengths, because Elbashir et al. teaches guidelines and sets forth that the results provide a rational basis for the design of siRNAs.

With regards specifically to the sense region comprising SEQ ID NO: 7 and the antisense region comprising a reverse complement of instant SEQ ID NO: 7, siRNAs of this genus are within the genus that would result from routine optimization of the guidelines/testing set forth by Elbashir et al., Tuschl et al., and Holen et al. Applicant

has not demonstrated any unexpected result for a siRNA comprising the instant sequences, wherein sequences within this genus would have resulted from the rational design of siRNAs to HIF-1α following the published guidance of Elbashir et al., Tuschl et al., and Holen et al.

In view of the availability of targeting guidelines, as taught by Elbashir et al. and Tuschl et al., and the known optimization of siRNA duplexes via walking the target sequence, as evidenced by Holen et al., one of skill would have been able to envision every siRNA directed to the instant target HIF-1α sequence. Although the relative activities would need to be experimentally determined, the majority of such siRNAs designed via the rules established in the art have some level of RNA interference activity.

As set forth in MPEP 2144.08, a species is obvious in view of the genus where one of skill would be able to immediately envision each species. Although the instant genus is large, one of skill would have been able to immediately envision each species of siRNA molecules targeted to RAD1 in view of the guidelines discussed above. It would have been obvious to one of skill to select any given siRNA targeted to HIF-1α based on the guidelines of Elbashir et al. and Tuschl et al., and the optimization of Holen et al. via shifting frame to yield optimal siRNAs.

One would have a reasonable expectation of success given that each of the modifications and linkers were known in the art at the time the invention was made to add benefits to siRNA molecules, as evidenced by both Reich et al. and Fosnaugh et al. One would reasonably expect for the modifications and structural elements of the siRNA

molecules of Fosnaugh et al. to yield the same benefits to the siRNA molecules targeted to HIF-1α of Reich et al.

Finally, one of skill in the art would have had a reasonable expectation of success at generating a siRNA duplex wherein the sense region comprises SEQ ID NO: 7 and the antisense region comprises the reverse complement of SEQ ID NO: 7 because Reich et al. discloses the instant target sequence and siRNA molecules directed to it; Elbashir et al. and Tuschl et al. teach design guidelines for siRNA molecules against any given mammalian target; and Holen et al. teaches walking a target sequence to optimize activity of the siRNA. Therefore, one would expect for the guidelines established in the art to result in siRNA molecules within the instant genus. Furthermore, Elbashir et al. teaches rational design guidelines for siRNA molecules including length and the presence or absence of overhangs.

Although the genus of possible siRNA molecules that would be produced by the guidelines of the prior art is very large, it is within the realm of routine optimization to determine optimal siRNA molecules from the genus. The genus of siRNA molecules directed to the instant target sequence is described in the art because the target sequence was known and guidelines were established for designing siRNAs to a given target. Therefore, one of skill in the art had the tools to aid and predict which siRNA molecules will have the required function, and can readily make and test the siRNAs for resultant RNAi activity, consistent with the published Written Description Guidelines (i.e. Example 12).

Thus in the absence of evidence to the contrary, the invention as a whole would

have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Claims 36, 38-42, 45-59, 62, and 63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reich et al. (WO 2004/042024 A2), , in view of Fosnaugh et al. (US 2003/0143732 A1), Elbashir et al. (The EMBO Journal, Vol. 20, No. 23, pages 6877-6888, 2001), Tuschl et al. (The siRNA user guide, 8/26/01 (on-line), retrieved 1/31/02, Max Planck Institute for Biophysical Chemistry, pages 1, 3, and 5, http://www.mpibpc.gwdg.de/abteilungen/100/105/siRNAuserguide.pdf), and Holen et al. (Nucleic Acids Research, 2002, Vol. 30, No. 8, pages 1757-1766), as explained in the rejection under 35 USC 103(a) above, further in view of Fire et al. (US 6,506,559).

The instant claims are directed to a small interfering RNA (siRNA) molecule that down regulates expression of a hypoxia-inducible factor 1α (HIF-1α) gene by RNA interference. The claims are further directed to structural requirements of the siRNA, linkers, modifications, terminal caps, vectors, and cells comprising the vectors.

It is noted that the instant claims are directed to a siRNA molecule that comprises a sense region and an antisense region, wherein the sense region "comprises" SEQ ID NO: 7 and the antisense region "comprises" a reverse complement of SEQ ID NO: 7. The instant rejection is based upon the comprising language, as the siRNA does not have any length limit as instantly recited. Recitation of "consists" or "is" a specific length, for example, would obviate this rejection.

Fire et al. teaches a method of inhibiting the expression of a target gene in a cell comprising introduction of a double-stranded RNA molecule in an amount sufficient to inhibit the expression of the target gene, wherein the double-stranded RNA has a first strand consisting essentially of a ribonucleotide sequence which corresponds to a nucleotide sequence of the target gene and a second strand consisting of a ribonucleotide sequence which is complementary to the nucleotide sequence of the target gene (see claim 1). Fire et al. teaches that the double-stranded RNA can be directly injected into the cell or extracellularly injected into the organism (see column 5). Fire et al. teach that the method may be used to introduce RNA into a cell for the treatment of a disease (see column 9) and that the invention is not limited to any type of target gene or nucleotide sequence (see column 11). Fire et al. exemplifies the method of dsRNA inhibition in *C. elegans* via RNA interference (see column 14). Fire et al. teaches that higher doses of the dsRNA resulted in more effective inhibition. Fire et al. teach that lipid-mediated carrier transport or chemical-mediated transport can be used to deliver the RNA molecules (see column 9). Fire et al. teach that double-stranded RNA-mediated inhibition has advantages both in the stability of the material to be delivered and the concentration required for effective inhibition (see column 3).

It would have been obvious to design a siRNA directed to HIF-1α, as explained in the rejection under 35 USC 103(a) above, comprising SEQ ID NO: 7 and a reverse complement thereof.

Furthermore, one would have been motivated to inhibit the expression of HIF-1α with a longer dsRNA because Fire et al. teaches that dsRNA molecules are utilized in

methods of inhibiting target gene expression and treating diseases via RNA interference. Armed with the knowledge of Fire et al., one would be motivated to utilize the method of Fire et al. to design the dsRNA of the method to span the entire open reading frame and therefore the resultant dsRNA molecule directed to HIF-1α would necessarily comprise the instantly recited sequences. Since Fire et al. teach that double-stranded RNA-mediated inhibition has advantages both in the stability of the material to be delivered and the concentration required for effective inhibition, one would have been motivated to utilize a dsRNA.

Since Fire et al. teaches a method of inhibiting target gene expression with dsRNA molecules and teaches the benefits of these molecules to other antisense approaches, one would have had a reasonable expectation of success in utilizing the long dsRNA molecules of the method of Fire et al. to target HIF-1α as Reich et al. has demonstrated targeting HIF-1α with siRNA molecules, wherein the long dsRNA would necessarily comprise the instant sequences.

Finally, one of skill in the art would have had a reasonable expectation of success at generating a siRNA duplex wherein the sense region comprises SEQ ID NO: 7 and the antisense region comprises a reverse complement of SEQ ID NO: 7 because Reich et al. teaches siRNA molecules to HIF-1α and Fire et al. teaches production of long dsRNA molecules that act via RNAi, wherein a long dsRNA molecule of Fire et al. directed to HIF-1α would comprise the instant sequences.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to AMY BOWMAN whose telephone number is (571)272-0755. The examiner can normally be reached on Monday-Thursday 6:00 - 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

AMY BOWMAN
Examiner
Art Unit 1635

/AMY BOWMAN/
Examiner, Art Unit 1635